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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
UNGAR, SUSAN NMN	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,211	ASP ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *15 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *2,3,7-12 and 14-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,4-6 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/13, 6/25, 7/1/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The Election filed March 15, 2004 in response to the Office Action of February 18, 2004 is acknowledged and has been entered. Claims 1-22 are pending in the application and Claims 2-3, 7-12, 14-22 and all limitations drawn to methods other than a method of treating breast cancer have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1, 4-6 and 13 drawn to a method of treating breast cancer are currently under prosecution.

2. The response to the restriction requirement of February 18, 2004 has been received. Applicant has elected Group I, claims 1. 4-6 and 13 for examination with traverse. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a).

Specification

3. The specification is objected to because of spelling errors, for example on p.4, lines 19 and 27. Examiner has made an effort to identify these informalities but applicant must carefully review the specification to identify and indicate where these informal errors may be found. Appropriate correction is required.

Oath or Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.0.

The oath or declaration is defective because the residence and post office address of Inventor Asp has been altered but that alteration has neither been dated nor initialed.

Trademarks

5. The use of the trademark trastuzumab has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Information Disclosure Statements

6. It is noted that Items 20 and 26 submitted with the Information Disclosure on June 26, 2002 have not been considered since neither a full translation nor a translated abstract appear to have been submitted with these references. Further, Reference 23 on the information disclosure statement submitted June 18, 2002 has been lined through because it duplicates a reference submitted in the information disclosure of June 26, 2002.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 13 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is drawn to a method for ameliorating cardiotoxic effects caused by trastuzumab when administered alone, which comprises administering an effective amount of dexrazoxane.

The specification teaches that an overview of clinical data indicates that the use of trastuzumab alone is sometimes associated with undesired cardiotoxocity, clinically expressed, as for anthracyclines, by a progressive decrease in cardiac systolic function or even by a serious damage of myocytes, mainly in the left ventricle and septum (p. 2, lines 18-23). The specification further teaches that the histomorphology of anthracycline-induced cardiotoxocity is characterized by multifocal vacuolar degeneration of myocytes and dilation of sarcoplasmic reticulum and transverse tubules has also been described, wherein for trastuzumab, the myocardial damage is generally more evident in the left ventricle and septum. While the underlying anthracycline-induced cardiotoxocity has not been conclusively determined, considerable evidence has accumulated indicating that cardiomyopathy is principally due to an iron-dependent free radical oxidative stress (para bridging pages 2-3). Although the mechanism by which dexrazoxane reduces anthracycline-induced cardiotoxocity has not been fully elucidates, it would appear that the compound, unlike other free radical scavengers, specifically disrupts the drug-iron complexes that can bind to DNA and membrane targets: for which the latter acts as a source for hydroxyl radicals. In addition, dexrazoxane can be expected to also effectively chelate adventitious iron (p. 3, lines 8-26). Even though several studies have been undertaken to learn the nature of trastuzumab-induced cardiotoxicity, its mechanisms of action, as well as the mechanism by which trastuzumab potentiates the cardiotoxic effects of anthracyclines, are still unclear and are not fully elucidated (p. 4, lines 8-13).

The specification further teaches that it has now been found that dexrazoxane can have cardioprotective efficacy not only on trastuzumab-induced myocardial damage, but also on myocardial damage caused by its concomitant or sequential administration with anthracycline (p. 4, lines 21-25). The specification states that a method for ameliorating cardiotoxic effects caused by trastuzumab when administered alone by administration of dexrazoxane is within the scope of the invention. The specification teaches that preclinical trials in a validated mouse model can be used to verify amelioration of cardiotoxocity of murine anti-HER2 antibodies in mice. The specification notes that the use of a murine HER2 antibody is needed because trastuzumab is specific for human and primate HER2 (p. 6, lines 12-25). The specification discloses a protocol for said preclinical trial (p. 7-10).

One cannot extrapolate the teaching of the specification to the enablement of the claims. Although the specification states that the use of trastuzumab alone is sometimes associated with undesired cardiotoxocity, clinically expressed, as for anthracyclines, by a progressive decrease in cardiac systolic function or even by a serious damage of myocytes, mainly in the left ventricle and septum (p. 2, lines 18-23), the specification goes on to specifically teach that the histomorphology of anthracycline-induced cardiotoxocity is characterized by multifocal vacuolar degeneration of myocytes and dilation of sarcoplasmic reticulum and transverse tubules has also been described, wherein for trastuzumab, the myocardial damage is generally more evident in the left ventricle and septum. Given the differences in the sites of damage, it would not appear that the mechanism of the putative cytotoxicity of trastuzumab is not the same as that of the anthracyclines. It is noted that the specification teaches that although the mechanism by which dexrazoxane

reduces anthracycline-induced cardiotoxocity has not been fully elucidated, it would appear that the compound, unlike other free radical scavengers, specifically disrupts the drug-iron complexes that can bind to DNA and membrane targets: for which the latter acts as a source for hydroxyl radicals. In addition, dexrazoxane can be expected to also effectively chelate adventitious iron (p. 3, lines 8-26). Given that the cytotoxic site of action of the anthracyclines appears to be different from that of trastuzumab, given that the mechanism of action of dexrazoxane is different that that of other free radical scavengers and that it appears to be anthracycline specific in that it disrupts the anthracycline/iron complex, it could not be predicted and would not be expected that dexrazoxane would function to inhibit the putative trastuzumab cardiotoxocity, given that neither the specification nor the art of record suggests that the antibody forms an iron complex or that its effects on the putative cardiotoxicity are through free radical formation involving iron. In additional, although the specification clearly states that it has now been found that dexrazoxane can have cardioprotective efficacy not only on trastuzumab-induced myocardial damage, but also on myocardial damage caused by its concomitant or sequential administration with anthracycline (p. 4, lines 21-25) there is no evidence, data or even sound scientific reasoning that would explain why or how this finding was made. In the absence of objective evidence, given the known iron-related mechanisms of dexrazoxane, given the lack of any nexus between trastuzumab and iron-related free radical formation, no one of ordinary skill in the art would believe it more likely than not that the invention would function as claimed simply based on the known cardioprotective effects of dexrazoxane in anthracycline chemotherapy patients. Further, although the specification suggests that a murine animal model, using murine HER2 antibodies

instead of trastuzumab can be used to verify amelioration of cardiotoxocity of murine anti-HER2 antibodies in mice and infers that this information could be extrapolated to the use of trastuzumab in man, there is neither information in the specification or in the art of record that any HER2 antibody is cardiotoxic in mice, nor is there information in the specification or in the art of record that any HER2 antibody other than trastuzumab is cardiotoxic in humans. Thus, it could be predicted that a murine model could be used to determine whether or not dexrazoxane has a protective effect, given that it is unknown whether or not any HER2 antibody other than trastuzumab is cardiotoxic. In particular, Sparano (Seminars in Oncology, 2001, 28(Suppl3)20-27, IDS item) specifically teaches that in monkeys treated with trastuzumab at doses more than 10-fold higher than in humans for up to 6 months, no cardiac toxicity was seen. Given this finding, one would question whether in fact trastuzumab alone is cardiotoxic in humans. Further, if it were to be determined that trastuzumab is cardiotoxic in humans, the difference in the effect of trastuzumab on a closely related species would clearly bring into question whether a correlation could be established between the findings in a mouse model using a different antibody and the effects of dexrazoxane on cardiotoxicity using trastuzumab in man.

In particular as drawn to the cardiotoxicity of trastuzumab, Nancy Cook-Bruns (Oncology, 2001, 61(suppl 2)58-66, IDS item), teaches that a retrospective analysis revealed a higher incidence of heart failure when Herceptin was combined with anthracyclines than expected with anthracyclines alone (see abstract). The authors find that patients who had not received prior anthracycline therapy showed a significantly lower level of cardiotoxicity. Of the 84 anthracycline-naïve patients in these clinical trials, only three developed heart

failure. All three patients were elderly, had a history of cardiac disease and improved with standard treatment for heart failure. These findings support that Herceptin has no inherent cardiotoxicity and does not directly lead to cardiac failure. Further, the authors teach that, in relation to the potentiation of anthracycline cardiotoxicity, it is possible that Herceptin may interfere with myocyte growth and repair after anthracycline-induced damage (p. 62, col 2). Further, Gianni (Annals of Oncology, 12(Suppl 2):S63-S68, 2001, IDS item) specifically discusses cardiac adverse events associated with Herceptin clinical trials, wherein the author puts forth a number of hypotheses to explain the cardiotoxicity. These include (a) that trastuzumab has inherent cardiac toxicity similar to that caused by anthracyclines, (b) trastuzumab amplifies the effects of anthracyclines on the heart through an additive or synergistic effect, (c) the cardiac toxicity of trastuzumab could represent an observational artifact due to the serial prospective clinic and instrumental monitoring of cardiac function that is common nowadays in many clinical trials in oncology. (p. 66). The author concludes that on going studies should determine the nature of the cardiotoxicity of trastuzumab (p. 67). Ewer et al (Seminars in Oncology, 1999, 26(Suppl 12), 96-101, IDS item) teach that If trastuzumab demonstrates inherent toxicity it will probably be best detected in clinical studies using cardiac biopsies. It is possible that the morphologic changes caused by trastuzumab may be different from those caused by anthracyclines. This possibility should be actively investigated (para bridging col 1 and 2, p. 100). The authors conclude that a better understanding of trastuzumab cardiotoxicity is essential.....the true risk of toxicity must be defined (p. 100, col 2). The authors speculate that trastuzumab toxicity may have inherent cardiotoxicity, may be caused by sequential stresses following

doxorubicin administration or may be an observational artifact that lead to an overestimation of trastuzumab cardiotoxicity. Finally, two years later Sparano (Seminars in Oncology, 2001, 28(Suppl 3)20-27, IDS item) specifically teaches that the pathogenesis of cardiac dysfunction associated with trastuzumab is unknown. trastuzumab has not been shown to localize to the heart in animal models. Furthermore, in monkeys treated with trastuzumab at doses more than 10-fold higher than in humans for up to 6 months exhibited no cardiac toxicity. No HER2 protein expression was demonstrated in myocardial tissue (p. 22). The association between trastuzumab-associated cardiac dysfunction and doxorubicin exposure suggest that trastuzumab may augment anthracycline-induced cardiac injury (p. 23, col 1). It is clear, that at the time the invention was made that contradictory findings were being reported. Nancy Cook-Bruns concluded that the findings support that Herceptin has no inherent cardiotoxicity and does not directly lead to cardiac failure. Gianni and Ewer et al put forth numerous hypotheses to explain adverse effects but it is clear that two years after the publication of the Ewer et al reference, it was unknown whether in fact trastuzumab had any inherent cardiotoxicity. Finally Sparano points out that trastuzumab does not localize to the heart in animal models, that it has no cardiotoxicity in a closely related animal monkey model and finally points to the association between trastuzumab-associated cardiac function and doxorubicin exposure. Given the above it is clear that it had not been established, at the time the invention was made, whether or not trastuzumab is in fact cardiotoxic. Since it was unknown whether or not trastuzumab was cardiotoxic, it could not be predicted that dexrazoxane would have any effect on trastuzumab-associated cardiotoxicity. The specification provides insufficient guidance with regard to these issues and provides no working

examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the claimed invention would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 1, 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Norton et al (25th Annual Meeting of the American Society of Clinical Oncology,

1999, 18:127) in view of Swain et al (J. Clinical Oncology, 1997, 15:133-1340, IDS item).

The claims are drawn to a method for treating a cancer, breast cancer, which comprises administering a therapeutically effective amount of trastuzumab to a patient in need thereof, in combination with an amount of dexrazoxane effective to ameliorate cardiotoxicity.

It is noted that the recitation of the term "comprising" is understood for examination purposes to mean that the treatment can comprise additional moieties.

Norton et al teach a method of treating breast cancer patients with a combination of trastuzumab and doxorubicin wherein it was found that simultaneous treatment with doxorubicin and trastuzumab is superior, in terms of overall survival, when compared to either doxorubicin alone or trastuzumab alone.

Norton et al teach as set forth above, but do not teach a method wherein the method comprises administration of dexrazoxane.

Swain et al teach that doxorubicin causes cumulative, dose-related progressive myocardial damage that may compromise cardiac function (p. 1333, col 10) and that Dexrazoxane (DZR) ameliorates the cardiomyopathy associated with anthracyclines, in particular doxorubicin (p. 1333). The reference further teaches that there was a striking survival advantage for patients who started DZR after they had received 300 mg/m^2 of doxorubicin (p. 1339, paragraph 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have combined the methods of Norton et al and Swain et al and to administer DZR in combination with trastuzumab and doxorubicin in order to ameliorate the cardiomyopathy known to be associated with the administration of doxorubicin. One would have been motivated to have

combined the methods of Norton et al and Swain et al and to administer DZR in combination with trastuzumab and doxorubicin because Swain et al specifically teach that doxorubicin causes cumulative, dose-related progressive myocardial damage that may compromise cardiac function and that Dexrazoxane (DZR) ameliorates the cardiomyopathy associated with anthracyclines, in particular doxorubicin . One would have had a reasonable expectation of success given the teaching in Swain et al that there was a striking survival advantage for patients who started DZR after they had received 300 mg/m^2 of doxorubicin.

11. No claims allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at 571-272-0841 The fax phone number for this Art Unit is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Susan Ungar
Primary Patent Examiner
May 1, 2004